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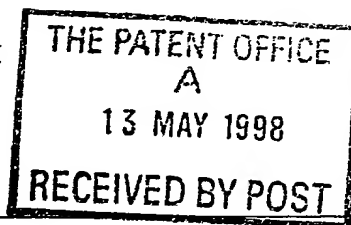
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Request for grant of a patent



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1 Your reference

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2 Patent application number

9810127.2

3 Full name, address and postcode of the applicant

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Patents ADP number

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State of incorporation

United Kingdom

4 Title of the invention

Prevention of Surgical Adhesions

5 Name of agent

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6 Priority applications

Country

Priority App No

Date of Filing

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7 Parent application (eg Divisional) Earlier Application No Date of Filing

8 Statement of Inventorship Needed? Yes

9 Number of sheets for any of the following (not counting copies of same document)

Continuation sheets of this form
Description
Claims
Abstract
Drawings

10

Handwritten signature

10 Number of other documents attached

Priority documents
Translations of priority documents
P7/77
P9/77
P10/77
Other documents

11 I/We request the grant of a patent on the basis of this application.

Signature Lisa P Brown

12 May 1998

12 Name and daytime telephone number of person to contact in the United Kingdom

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PREVENTION OF SURGICAL ADHESIONS

5 This invention relates to the prevention of surgical adhesions, and in particular to adhesions taking place in serous cavities including the peritoneum, the pericardium, the plura and synovial cavities such as joints and tendons and to adhesions following spinal and/or cranial operations. Reference will be made hereinbelow to the prevention of adhesions in the peritoneum but it should be understood that the present invention has applicability in connection with other serous cavities in both humans and animals.

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Abdominal surgery is a rapidly changing field. Many forms of open surgery are being increasingly replaced by laparoscopic procedures. Although considerable immediate post-surgical benefits have been demonstrated to follow from laparoscopic surgery, the incidence of adhesions has not decreased. The severe
15 drying of the mesothelium which results from prolonged exposure of the peritoneum to dry gases (pneumoperitoneum of 2-4 hours), may give rise to a higher incidence of global peritoneal adhesions than has hitherto been encountered in open surgery. Many gynaecologists with long experience of laparoscopic surgery consider that both open and closed surgery have equally high incidences of adhesions.

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WO 92/21354 describes a surgical adhesion as the attachment of organs or tissues to each other through scar tissue. A formation of scar tissue is described as a normal sequel to surgery or other tissue injury and is required for proper wound healing. In some cases, however, the scar tissue overgrows the intended region and creates
25 surgical adhesions. These scar tissue surgical adhesions restrict the normal mobility and function of affected body parts. The invention disclosed in WO 92/21354 is based on the discovery that anionic polymers effectively inhibit invasion of cells associated with detrimental healing processes, ie, fibrosis, and scarring. In particular, certain inhibitory anionic polymers are useful to inhibit fibroblast invasion, thus
30 regulating the healing process and preventing fibrosis. Anionic polymers specified in WO 92/21354 include dextran sulfate, pentosan polysulfate as well as natural

proteoglycans, or the glycosaminoglycan moieties of proteoglycans, including dermatan sulfate, chondroitin sulfate, keratan sulfate, heparan sulfate, heparin and alginate.

5 By attempting to inhibit fibroblast invasion, the approach of WO 92/21354 is one of post-adhesion treatment since fibroblast invasion is a later stage, that is to say, it occurs after formation of the adhesion. The invention of WO 92/21354 attempts to prevent the adhesion becoming permanent. By contrast the present invention is concerned with the prevention of the occurrence of an adhesion.

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According to a first aspect of the present invention there is provided a method of preventing or reducing the incidence of post-operative adhesions in or associated with a body cavity, which comprises introducing into the body cavity an aqueous solution or suspension or gel formulation containing the polysaccharide dextrin.

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The term "dextrin" means a glucose polymer which is produced by the hydrolysis of starch and which consists of glucose units linked together by means mainly of α -1,4 linkages. Typically dextrans are produced by the hydrolysis of starch obtained from various natural products such as wheat, rice, maize and tapioca. In addition to α -1,4 linkages, there may be a proportion of α -1,6 linkages in a particular dextrin, the amount depending on the starch starting material. Since the rate of biodegradability of α -1,6 linkages is typically less than that for α -1,4 linkages, it is preferred that, for many applications, the percentage of α -1,6 linkages is less than 10% and more preferably less than 5%.

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Any dextrin is a mixture of polyglucose molecules of different chain lengths. As a result no single number can adequately characterise the molecular weight of such a polymer. Accordingly, various averages are used, the most common being the weight average molecular weight (Mw) and the number average molecular weight (Mn). Mw is particularly sensitive to changes in the high molecular weight content

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of a polymer whilst Mn is largely influenced by changes in the low molecular weight content of the polymer.

5 It is preferred that the Mn of the dextrin is in the range of from 1,000 to 30,000 and ideally the Mw is in the range of from 3,000 to 50,000. More preferably, the Mn is from 3,000 to 8,000 and the Mw is from 5,000 to 50,000.

10 The term "degree of polymerisation" (DP) can also be used in connection with polymer mixtures. For a single polymer molecule, DP means the number of polymer units. For a mixture of molecules of different DP's, weight average DP and number average DP correspond to Mw and Mn. In addition, DP can also be used to characterise a polymer by referring to the polymer mixture having a certain percentage of polymers of DP greater than a particular number or less than a particular number.

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It is preferred that the dextrin contains more than 15% of polymers of DP greater than 12 and, more preferably, more than 50% of polymers of DP greater than 12.

20 The dextrin used in the present invention is water soluble or at least forms a suspension in water or a gel formulation. The dextrin used in this invention may be in the form of either unsubstituted dextrin (as obtained by the hydrolysis of starch) or may be substituted by one or more different groups. The substituents may be negatively charged groups, for instance, sulfate groups, neutral groups, or positively charged groups, for instance, quaternary ammonium groups. In the case where the
25 substituent group is sulfate, it is preferred that the sulfated polysaccharide contains at least one sulfate group per saccharide (glucose) unit.

30 The present invention also provides a composition comprising an aqueous solution or suspension or gel formulation of the polysaccharide dextrin in which the amount of dextrin is effective to prevent or reduce the incidence of post-operative adhesions.

The present invention further provides the use of a composition in the prevention or reduction of the incidence of post-operative adhesions, the composition comprising an aqueous solution or suspension or gel formulation of the polysaccharide dextrin.

5 The present invention further provides the use of the polysaccharide dextrin in the manufacture of a composition comprising an aqueous solution or suspension or gel formulation of dextrin for preventing or reducing post-operative adhesions in humans and animals.

10 Dextrin is a useful material for the production of an adhesion-preventing composition because, *inter alia*, it is non-toxic, cheap and has the ability to hold fluid in a body cavity. It is also readily metabolisable within the body.

Preferably, a composition of the invention is applied to the appropriate cavity or area
15 after the operation has been carried out.

Preferably, the composition of the present invention is allowed to remain in the body cavity for a minimum of 2 to 3 days and particularly over the period during which fibrin exudation is at a maximum. More preferably, the composition should remain
20 in the body cavity for a period of up to 7 to 8 days in order to allow restoration of non-stick surfaces (mesothelium regeneration).

Preferably, a composition of the invention should be applied to the body cavity in a volume large enough to keep the surfaces apart. For the peritoneum, the volume
25 should preferably be in the range 500-2000 ml and, more preferably, about 1000 ml-1500 ml.

Preferably, the composition should be applied to the appropriate body cavity or area in differing concentrations ideally over a concentration range of 4-20% and more
30 ideally said concentration range is selected for a specified time span, even more ideally the concentration range is selectively altered over a period of time.

Preferably, the composition should include a concentration of dextrin which is such that the fluid largely holds in place over the period it resides in the cavity. Where a composition includes 7% by weight of dextrin then a suitable dwell period for one infusion might be of the order of 2 to 3 days. A high concentration is liable to cause
5 ingress of fluid. A second infusion at day 3 may extend the total dwell period from 6 to 7 days.

Alternatively, a composition having a dextrin concentration of from 12 to 15% by weight may be used in a smaller volume (perhaps about 750 ml) and will be subject
10 to ingress of fluid. However a single infusion might be sufficient for the full 6 to 7 day period.

Comparing dextrin with dextran, the latter has relatively poor biocompatibility. It is subject to immunological hypersensitivity due to its concentration in lymph nodes
15 and its lack of metabolisability. At best, a dextran solution or suspension will act not so much to separate surfaces and therefore prevent adhesions but simply as a lubricant.

The use of a solution or suspension or gel formulation of dextrin is also advantageous
20 by comparison with a prior art technique which makes use of synthetic films in the form of patches which are applied to particular areas where maximum damage has occurred. However, in the case of a body cavity, such as the peritoneum, the damage is liable to occur as well at a distance from the operative site, especially in laparoscopy, due to the drying which takes place. In some instances global damage
25 over an area of as much as two square metres can take place.

In responding to a wound, the body causes circulating fibrinogen to form fibrin and it is this production of fibrin which is associated with the formation of adhesions. Calcium ions are required to polymerise fibrinogen to fibrin and, accordingly, a
30 composition of the present invention may include a calcium binding agent such as EDTA or sodium citrate.

A composition of the present invention may include a suitable lubricant such as a phosphospholipid.

5 A composition of the present invention may include a hyaluronate or glycosaminoglycan, a material which is associated with serosal lubrication and which has strong anti-adhesive properties. In this case the dextrin solution or suspension or gel formulation is effective in spreading the hyaluronate throughout the whole peritoneum.

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A composition of the present invention may include an antibiotic agent or a material which is associated with preventing an infection or build up of bacteria or foreign bodies or the like. A composition including such an agent/material would be particularly advantageous in prevention or amelioration of pelvic inflammatory disease.

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The present invention provides a preferred composition comprising an aqueous solution or suspension or gel formulation of dextrin, one or more phosphospholipids and hyaluronate. Such a composition is not only highly effective in preventing adhesions but also has a good shelf life.

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Mesothelial secretion of prostacyclin has been demonstrated and this activity enhances the non-stick properties of the mesothelium. The present invention provides a composition comprising dextrin together with prostacyclin or an analogue thereof.

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According to a second aspect of the invention there is provided a biocompatible, bioresorbable, and non-toxic post-operative adhesion prevention kit for surgical use in humans or animals, comprising an aqueous solution or suspension or gel formulation of dextrin as hereinbefore described, and optionally or additionally comprising a calcium binding agent as hereinbefore described and/or a suitable

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lubricant as hereinbefore described and/or prostacyclin or an analogue thereof as hereinbefore described and/or an antibiotic agent as hereinbefore described..

EVIDENCE IN SUPPORT OF THE INVENTION

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PROTOCOL:

Animals: One hundred thirty, female New Zealand White rabbits, 2.4-2.7 kg, were purchased from Irish Farms (Norco, CA) and quarantined in the USC Vivaria for at least 2 days prior to use. Ten rabbits were randomised into thirteen treatment groups prior to initiation of surgery. The rabbits were housed on a 12:12 light:dark cycle with food and water available *ad libitum*.

Materials: The solutions (7.5% [wt/vol] icodextrin-Lot # 98A06G33, 20% [wt/vol] icodextrin-Batch # SP184772 and placebo (electrolyte solution for icodextrin)-Batch # SP184829 were supplied by ML Laboratories Plc. Icodextrin is a [1 → 4] - α - Glucan having more than 85% of its molecules with molecular weights between 1,640 - 45,000 with a weight average molecular weight of approximately 20,000. The placebo electrolyte solution contained 5.4g sodium chloride, 4.5g sodium lactate, 257 mg calcium chloride, 51 mg magnesium chloride in 1 litre water for injection. The sutures used to close the muscle and skin were 3-0 coated Dexon II suture (Davis and Geck, Manati, PR).

Double Uterine Horn Model: Rabbits were anaesthetised with a mixture of 55 mg/kg ketamine hydrochloride and 5 mg/kg Rompum intramuscularly. Following preparation for sterile surgery, a midline laparotomy was performed. The uterine horns were exteriorised and traumatised by abrasion of the serosal surface with gauze until punctate bleeding developed. Ischaemia of both uterine horns was induced by removal of the collateral blood supply. The remaining blood supply to the uterine horns was the ascending branches of the utero-vaginal arterial supply of the myometrium. At the end of surgery, 10 to 75 ml (10, 25, 50, 75 ml) of 7.5% or 20% icodextrin, 10 or 75 ml placebo or no treatment (control) was administered. After 7

days, the rabbits were terminated and the percentage of the area of the horns adherent to the various organs was determined. In addition, the tenacity of the adhesions was scored using the following system:

- 5 0 = No adhesions;
 1 = Mild, easily dissectable adhesions;
 2 = Moderate adhesions; non-dissectable, does not tear the organ;
 3 = Dense adhesions; non-dissectable, tears organ when removed.

- 10 In addition an overall score which takes into account all of the above data was given to each rabbit. The following scoring system was used:

- 0 No adhesions;
 0.5+ Light, filmy pelvic adhesions involving only one organ, typically only
15 1 or 2 small adhesions;
 1.0+ Light, filmy adhesions, not extensive although slightly more extensive
 than 0.5;
 1.5+ Adhesions slightly tougher and more extensive than a 1 rating;
 2.0+ Tougher adhesions, a little more extensive, uterine horns usually have
20 adhesions to both bowel and bladder;
 2.5+ Same as 2, except the adhesions are usually not filmy at any site and
 more extensive;
 3.0+ Tougher adhesions than 2, more extensive, both horns are attached to
 the bowel and bladder, some movement of the uterus possible;
25 3.5+ Same as 3, but adhesions slightly more extensive and tougher;
 4.0+ Severe adhesions, both horns attached to the bowel and bladder,
 unable to move the uterus without tearing the adhesions.

- 30 The rabbits were scored by two independent observers that were blinded to the prior treatment of the animal. If there was disagreement as to the score to be assigned to an individual animal, the higher score was given.

Statistical Analysis: The tenacity and overall scores were analysed by rank order analysis and analysis of variance on the ranks. The percentage area of the horns involved to the various organs was compared by Student's t test. The data from the incidence of adhesion formation was analysed by Chi square analysis. The comparison with placebo shown on Table 14 was done between the 10 ml placebo group and data from animals which received 10-25 ml of icodextrin or between the 75 ml placebo group and data from animals which received 50 or 75 ml icodextrin.

10 RESULTS: One rabbit from the group treated with 50 ml 20% icodextrin died postoperatively without evidence of inflammation or oedema at necropsy and was replaced. During the postoperative evaluation of the rabbits, it was noted that several rabbits given the higher volumes of icodextrin had "bulging" abdomens for the first few postoperative days. This occurred in 3 rabbits which received 75 ml or 7.5%
15 icodextrin and 8 rabbits which received 75 ml of 20% icodextrin. The bulging was observed for 24 hours in the rabbits which received 7.5% icodextrin and 48-72 hours in the rabbits which received 20% icodextrin. This bulging was not observed in the group of rabbits which received 75 ml of placebo. No excess fluid was observed in any icodextrin or placebo-treated rabbits at necropsy. One rabbit, which received 75
20 ml of 20% icodextrin, had a small amount of subcutaneous fluid at necropsy.

The effect of icodextrin on the formation of adhesions in this rabbit model can be found in Tables 1-13. The effect of icodextrin on the incidence of adhesions can be found in Table 14. For each site, the extent and tenacity (tenacity in parentheses) of
25 the adhesions between the horn and that site were given. In the final row of each column (with the exception of the column on the far right), the mean and standard error of the mean for the extent score for each site is given. In the final row of the final column, the mean and standard error of the mean of the ranks is given. If an extent or rank order was reduced compared to control ($p \leq 0.05$), a * is in the
30 appropriate row. At higher volumes (25 to 75 ml) of icodextrin, there was a significant reduction in the formation of adhesions. However, no difference between

the 7.5% and 20% solutions was noted in this study. This efficacy is in the absence of inflammation noted with some materials implanted intraperitoneally.

In conclusion results demonstrated that high volumes of icodextrin (both percentages) were highly efficacious in the reduction of adhesion formation in this model with efficacy noted after administration of 50 ml or 75 ml of icodextrin. The lower volumes of icodextrin have less effect and the placebo had no effect on adhesion formation. Thus we have demonstrated that the composition of the present invention is effective in reducing the incidence of post-operative adhesion formation.

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